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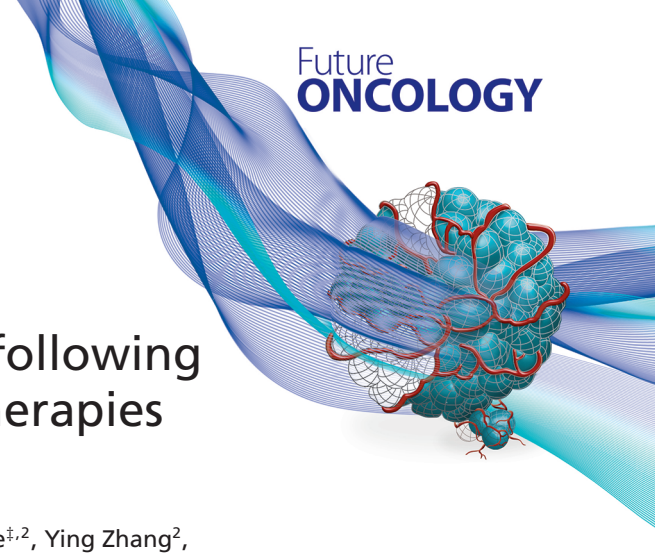

Treatment patterns and outcomes following disease progression on anti-PD-1 therapies for advanced melanoma

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Background: Anti-PD-1-based therapies prolong survival in advanced melanoma, but disease progression is common. This study evaluated treatment patterns and overall survival (OS) after anti-PD-1 progression. **Methods:** Retrospective data from patients with advanced melanoma and progression on anti-PD-1 treatment between 2014 and 2019 were taken from Flatiron Health, which reflects largely community practice. Treatment patterns and OS were analyzed for *BRAF* mutant (mt) and wild-type (wt) subgroups; OS was also examined across all patients. **Results:** Progression following anti-PD-1 was recorded for 679 patients. Median OS ranged from 5.0 to 11.3 months. Of 275 *BRAF*mt and 374 *BRAF*wt patients, 113 (41.1%) and 228 (61.0%) received no subsequent therapy, respectively. However, 48.4% of *BRAF*mt and 57.8% of *BRAF*wt patients continued anti-PD-1 treatment beyond progression. **Conclusion:** This real-world study underscores the need for effective treatments for advanced melanoma post-progression on anti-PD-1 therapy.

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Keywords: cancer progression • immunotherapy • melanoma • survival • treatment patterns

Melanoma is the most lethal form of skin cancer, and incidence has risen rapidly over recent decades [1,2]. Advanced melanoma is highly aggressive and associated with a poor prognosis. From 2010 to 2016, the Surveillance, Epidemiology, and End Results Program estimated that 66.2% of patients whose initial diagnosis was stage III melanoma, and just 27.3% of patients whose initial diagnosis was stage IV melanoma were expected to survive the 5-year mark [3].

Treatment for advanced melanoma has evolved considerably in recent years with the development of immunotherapy and targeted therapy. Checkpoint inhibition, a type of immunotherapy, has become a cornerstone of the melanoma treatment armamentarium for oncologists. Examples of checkpoint inhibitors include anti-PD-1 and CTLA-4 inhibitors. In clinical trials, these treatments have been found to be more effective than chemotherapy and are associated with prolonged progression-free survival (PFS) and overall survival (OS) [3–5]. Additional treatment options exist for patients with advanced melanoma who have a mutation in the *BRAF V600* gene (approximately 50%) [6]; targeted *BRAF*/*MEK* inhibitors have been found to improve clinical outcomes in this population [7–9].

Despite the clinical success of anti-PD-1 immunotherapies, there is still a large proportion of patients that fails to respond to these therapies initially (i.e., primary resistance) or respond but later relapse (i.e., acquired resistance) [10–12]. Data from clinical trials indicate a response rate of approximately 33–50% with first-line, single-agent anti-PD-1 therapy [13–16] and up to 60% for nivolumab plus ipilimumab [13,14,17]. Many patients thus need subsequent treatment in the second line, but no standard of care currently exists. Recent studies have shown that treatment with ipilimumab or retreatment with anti-PD-1 therapies in combination with ipilimumab are viable options for patients who have progressed on prior anti-PD-1 treatment [18–20]. Patients with a *BRAF V600* mutation (*BRAF*mt) with disease progression on first-line anti-PD-1 therapies frequently receive *BRAF* + *MEK* inhibitor therapy [21,22].

Future Medicine

Few studies have examined OS after the point of disease progression on anti-PD-1 therapy, although a recent retrospective study of patients with advanced melanoma found the median OS after disease progression on anti-PD-1 therapy to be 6.8 months [23]. Another study [24] examined patients retreated with immunotherapy following disease progression on initial anti-PD-1 therapy; OS at 1 year after the start of retreatment was 57% for patients treated with ipilimumab plus anti-PD-1 therapy, compared with 38% for ipilimumab therapy alone.

It is important to understand the real-world treatments and outcomes of patients with advanced melanoma who have experienced disease progression on anti-PD-1 therapy. Therefore, the aim of this study was to better understand treatment patterns and OS estimates after disease progression on anti-PD-1 therapies, overall and in the *BRAF*mt and *BRAF* wild-type (*BRAF*wt) populations.

Methods

Data Source

The Flatiron Heath database was used for this retrospective cohort study. Flatiron Health is a nationwide, longitudinal, demographically and geographically diverse database derived from deidentified electronic health record (EHR) data. At the time of the analyses, the database contained data from more than 280 cancer clinics (~800 sites of care) and more than 2.2 million US cancer patients [25]. Deidentified patient-level data include structured and unstructured data, curated via technology-enabled abstraction. Disease progression was identified from records indicating that the treating clinician had concluded that there had been tumor growth or worsening of the melanoma. A custom data extract was constructed, including patients with advanced melanoma. Patients had a diagnosis of melanoma (International Classification of Diseases, 9th Revision [ICD] 172.x or ICD, 10th Revision [ICD-10] C43x or D03x), pathologic stages III or IV at initial diagnosis or locoregional or distant recurrence following diagnosis at an earlier stage of disease and two clinic encounters in the Flatiron database. Patients with noncutaneous types of melanoma (ocular, subungual, mucosal, palmar and plantar) were excluded, as were those with a diagnosis of a primary cancer type other than melanoma, basal or squamous cell skin cancer or carcinoma *in situ* of the prostate, cervix or breast before the date of disease progression during anti-PD-1 therapy.

Study data complied with US patient confidentiality requirements. Because the study used only existing deidentified patient records, Institutional Review Board approval and patient informed consent were not required.

Study population

The study cohort included patients aged ≥18 years diagnosed with advanced melanoma and who received anti-PD-1 treatment at any line of therapy (LOT). Included patients experienced disease progression on treatment with anti-PD-1 therapy, as a single agent or in combination (most often with ipilimumab), or died without having a record of disease progression while on treatment. Patients were excluded for having been treated with an investigational agent for cancer during or before the first anti-PD-1 LOT. Included patients met all inclusion and exclusion criteria from 1 September 2014 to 30 November 2019.

The study index date was defined as the first recorded date of disease progression (excluding pseudo-progression or mixed disease progression) at least 14 days after the start of the first anti-PD-1 LOT and before the start of any subsequent LOTs. Patients were followed until death or their last visit before data cutoff (31 May 2020).

In patients who died without a record of disease progression while on anti-PD-1 therapy, an index date based on disease progression could not be determined. Therefore, these patients were removed from the main analyses and their baseline characteristics were summarized separately.

Study variables

Baseline demographic and clinical characteristics – including tumor status, number and type of prior LOTs, disease characteristics, *BRAF* status, time between the start of the first anti-PD-1 LOT and the disease progression date, as well as evidence of disease progression (radiographic, pathologic or clinical assessment) – were extracted from the EHR.

Outcomes

Treatment pattern data were extracted following disease progression on anti-PD-1 therapy, including subsequent treatment type and continued time on the anti-PD-1 therapy following the disease progression event (i.e., treatment beyond disease progression). The OS was calculated from the date of anti-PD-1 disease progression to the date of death. In patients with no record of death, OS was censored at the last visit in the study period.

Statistical analysis

Study measures, including baseline characteristics and treatment patterns, were summarized with descriptive statistics. Mean, standard deviation (SD), median and range were reported for continuous measures. Categorical measures were summarized using frequencies and percentages. The median OS with a 95% CI was estimated using Kaplan–Meier methods. Analyses were conducted separately for patients with and without *BRAF* mutations due to expected differences in treatments and outcomes between these two patient groups. In the *BRAF*mt group, analyses were also run in a subgroup of patients who had treatment with *BRAF* therapy (with or without an *MEK* inhibitor) before or during their index LOT (the first LOT containing an anti-PD-1 agent). Sensitivity analyses for OS, adding the patients who died without a record of disease progression while on anti-PD-1 therapy, were performed using a disease progression date imputed as the median time from anti-PD-1 initiation to disease progression among patients with the same *BRAF* status who had a record of disease progression. The imputed disease progression date was set to the death date for patients who died before the median time to disease progression. An additional sensitivity analysis examined OS separately for patients with and without further treatment with the anti-PD-1 beyond progression.

Results

Patient attrition

A total of 6256 patients with advanced melanoma were identified, of whom 2751 had a treatment regimen at any LOT containing an anti-PD-1 therapy. Of those patients, 1373 had a record in the database of progression or death during the cohort identification period. After applying the remaining inclusion and exclusion criteria, there were 1035 patients; 356 (34.4%) died without a record of disease progression, leaving 679 patients for the primary analyses (Figure 1). Of these, 275 and 374 had *BRAF*mt and *BRAF*wt melanoma, respectively, with 30 patients having unknown *BRAF* status.

Overall population

Baseline demographic & clinical characteristics

In the overall cohort of 679 patients, the median age was 68 years; 68.0% were male (Table 1). The majority (84.8%) of patients were white, and most (90.0%) were treated in a community practice. At initial melanoma diagnosis, most of these patients with advanced melanoma had stage IV disease (33.9%), followed by stage II (19.4%), stage III (19.3%) and stage I (9.0%). One patient (0.1%) had stage 0 disease, and 18.3% of patients had an unknown stage. Diagnosis codes for brain metastases were present in 20.3% of patients prior to their disease progression date, although this may have been under-reported in the EHR. Most patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1 (27.0% at ECOG 0; 29.9% at ECOG 1) at or within 6 months before the index disease progression date, and 17.8% had an ECOG PS of 2 or higher; ECOG PS was unknown for 25.3% of patients (Table 1).

Overall survival

Median OS from the index disease progression date was 11.3 months (95% CI: 9.9–12.5) in the primary analysis, which includes only those 679 patients with a recorded disease progression date (Figure 2). When adding the 356 patients who died before a record of disease progression to the primary cohort, the median OS was reduced from 11.3 to 5.0 months (95% CI: 4.2–6.2).

BRAFmt cohort

Baseline demographic, clinical & treatment characteristics

Among the 275 patients with *BRAF*mt, the median age was 65 years (Table 1). The most common disease stages at initial melanoma diagnosis were stage IV (30.5%) and stage III (21.8%), with 10.5 and 17.1% at stages I and II, respectively, and 20.0% with unknown stage. Diagnosis codes for brain metastases were present in 25.8% of patients before their disease progression date (Table 1).

Anti-PD-1 treatment occurred during the first LOT for 74.9% of patients. The most common treatment received before the index LOT was *BRAF* therapy with or without a *MEK* inhibitor (21.8%) or anti-CTLA-4 monotherapy (3.6%; Figure 3). Patients received nivolumab and ipilimumab combination therapy (33.1%), pembrolizumab monotherapy (30.5%) or nivolumab monotherapy for their index LOT (26.5%; Figure 3). The median time from start of the index LOT until the disease progression date was 2.5 months.

Table 1. Baseline demographic and clinical characteristics for patients with advanced melanoma by *BRAF* status.

Baseline	Overall (n = 679)	*BRAF*mt (n = 275)	*BRAF*wt (n = 374)
Demographic characteristic			
Age (years) at index date			
Median (IQR)	68 (58–77)	65 (52–74)	71 (61–79)
Sex			
Male	462 (68.0%)	182 (66.2%)	261 (69.8%)
Female	217 (32.0%)	93 (33.8%)	113 (30.2%)
Race			
White	576 (84.8%)	243 (88.4%)	310 (82.9%)
Black or African American	6 (0.9%)	2 (0.7%)	4 (1.1%)
Asian	1 (0.1%)	0 (0.0%)	1 (0.3%)
Other	55 (8.1%)	13 (4.7%)	39 (10.4%)
Unknown	41 (6.0%)	17 (6.2%)	20 (5.3%)
Practice type			
Academic	68 (10.0%)	39 (14.2%)	28 (7.5%)
Community	611 (90.0%)	236 (85.8%)	346 (92.5%)
Index year			
2015	36 (5.3%)	14 (5.1%)	22 (5.9%)
2016	107 (15.8%)	41 (14.9%)	58 (15.5%)
2017	162 (23.9%)	69 (25.1%)	90 (24.1%)
2018	220 (32.4%)	85 (30.9%)	125 (33.4%)
2019	154 (22.7%)	66 (24.0%)	79 (21.1%)
Clinical characteristic			
Time (months) from diagnosis to index date			
– From initial melanoma diagnosis			
Median (IQR)	20.4 (7.6–45.7)	21.7 (8.2–53.1)	20.2 (7.5–44.8)
– From first diagnosis of advanced melanoma			
Median (IQR)	7.8 (3.9–16.1)	7.9 (3.9–15.3)	7.8 (3.7–16.8)
– Stage at initial melanoma diagnosis			
0	1 (0.1%)	0 (0.0%)	1 (0.3%)
I	61 (9.0%)	29 (10.5%)	30 (8.0%)
II	132 (19.4%)	47 (17.1%)	76 (20.3%)
III	131 (19.3%)	60 (21.8%)	64 (17.1%)
IV	230 (33.9%)	84 (30.5%)	137 (36.6%)
Unknown	124 (18.3%)	55 (20.0%)	66 (17.6%)
– Presence of brain metastases on or before index date[†]			
Yes	138 (20.3%)	71 (25.8%)	65 (17.4%)
No/unknown	541 (79.7%)	204 (74.2%)	309 (82.6%)
– ECOG performance status; measurement on the index date or closest within 6 months earlier			
0	183 (27.0%)	73 (26.5%)	100 (26.7%)
1	203 (29.9%)	81 (29.5%)	115 (30.7%)
2	96 (14.1%)	40 (14.5%)	52 (13.9%)
3	19 (2.8%)	5 (1.8%)	10 (2.7%)
4	6 (0.9%)	2 (0.7%)	3 (0.8%)
Unknown	172 (25.3%)	74 (26.9%)	94 (25.1%)

Cell entries show n (%), unless otherwise specified. Patients with unknown *BRAF* status are excluded from the *BRAF*-stratified columns.
[†]Presence of brain metastases may be under-reported.
ECOG: Eastern Cooperative Oncology Group; IQR: Interquartile range; mt: Mutation; wt: Wild-type.

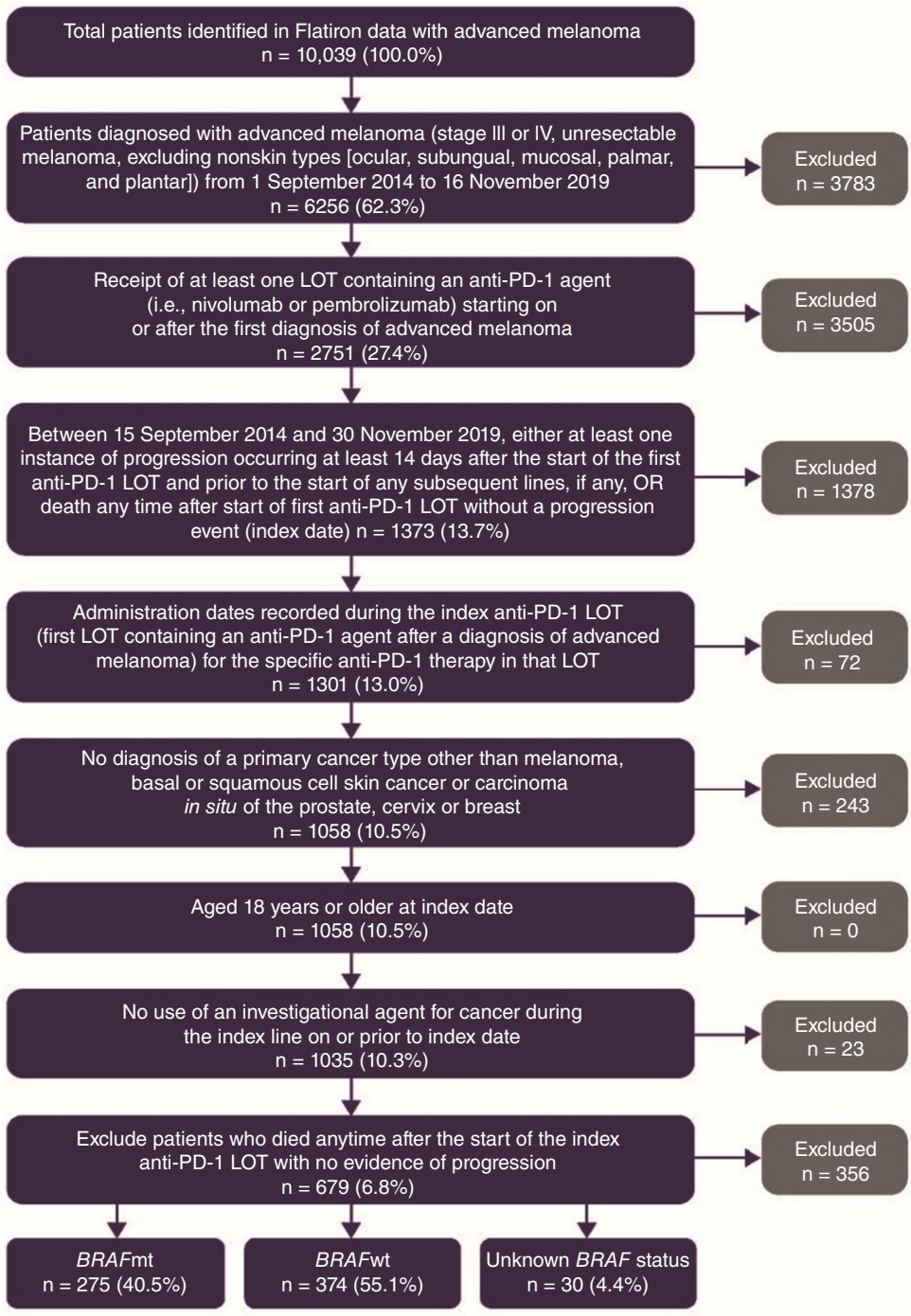

Figure 1. Study attrition for the anti-PD-1-treated advanced melanoma cohort. Index date is defined as the first date of progression (not including pseudo progression or mixed progression) occuring at least 14 days after the first line of therapy containing an anti-PD-1 and prior to any subsequent lines of therapy.
LOT: Line of therapy; NA: Not available; Mt: Mutation; Wt: Wild-type.

First subsequent therapy treatment patterns

More than one-third of patients (41.1%) had no subsequent treatment (i.e., no new LOT initiated) after their index LOT (Figure 3). In those patients with a subsequent treatment, the most common therapy received was *BRAF*-targeted therapy, alone or in combination with an *MEK* inhibitor (36.7%). Of those without a subsequent treatment, just over one-third (38.9%) had received *BRAF* therapy as part of or before their index LOT.

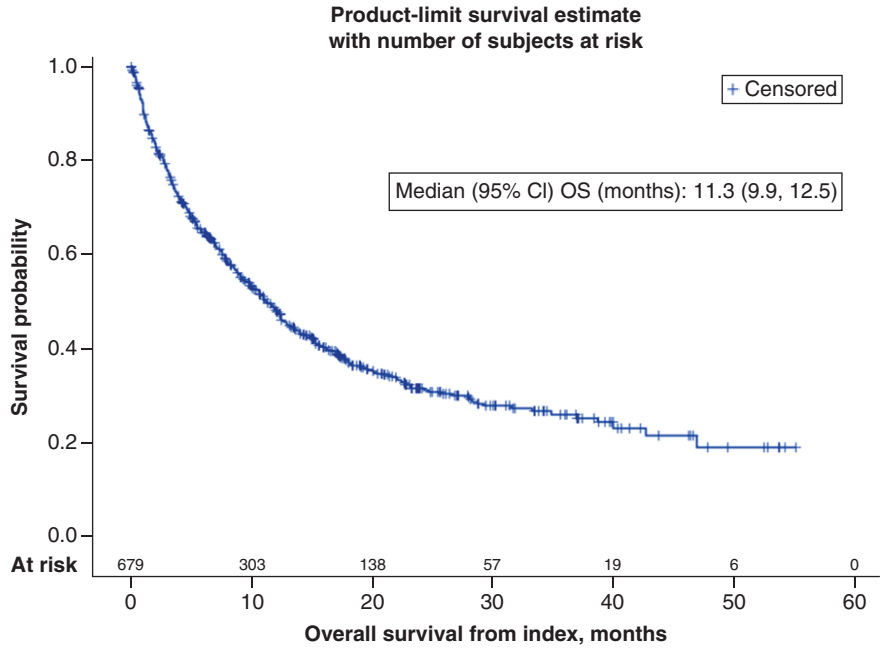

Figure 2. Overall survival from the index date, total cohort. The index date was the date of disease progression on the index anti-PD-1 line of therapy.
OS: Overall survival.

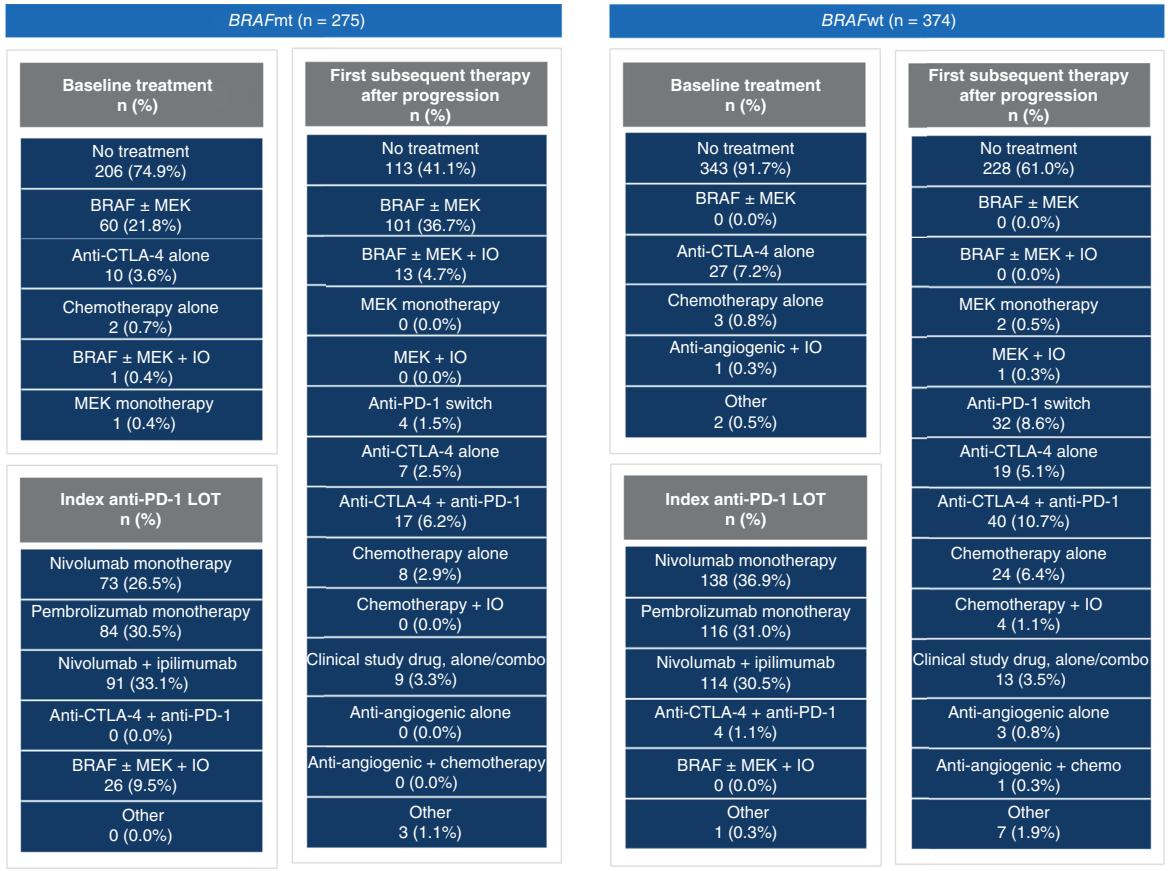

Figure 3. Treatment patterns by *BRAF* status.
IO: Immunotherapy; LOT: Line of therapy; mt: Mutation; wt: Wild-type.

Table 2. Follow-up duration and further treatment with index anti-PD-1 after index disease progression event.

	*BRAF*mt		*BRAF*wt	
	Those with a subsequent therapy	Those without a subsequent therapy	Those with a subsequent therapy	Those without a subsequent therapy
Follow-up duration (months)				
n	162	113	146	228
Median (IQR)	10.9 (5.7–19.0)	3.9 (1.0–16.5)	9.5 (4.7–17.7)	6.5 (1.8–16.8)
Time (months) from index date to discontinuation of index anti-PD-1 treatment for patients with at least one administration of index anti-PD-1 after progression				
n (%) with at least one administration	66 (40.7%)	67 (59.3%)	72 (49.3%)	144 (63.2%)
Median (IQR)	1.3 (0.7–6.0)	8.8 (1.3–17.1)	2.3 (0.6–4.3)	6.2 (1.4–15.6)

Patients with unknown *BRAF* status are excluded from the *BRAF*-stratified columns.
IQR: Interquartile range; mt: Mutation; wt: Wild-type.

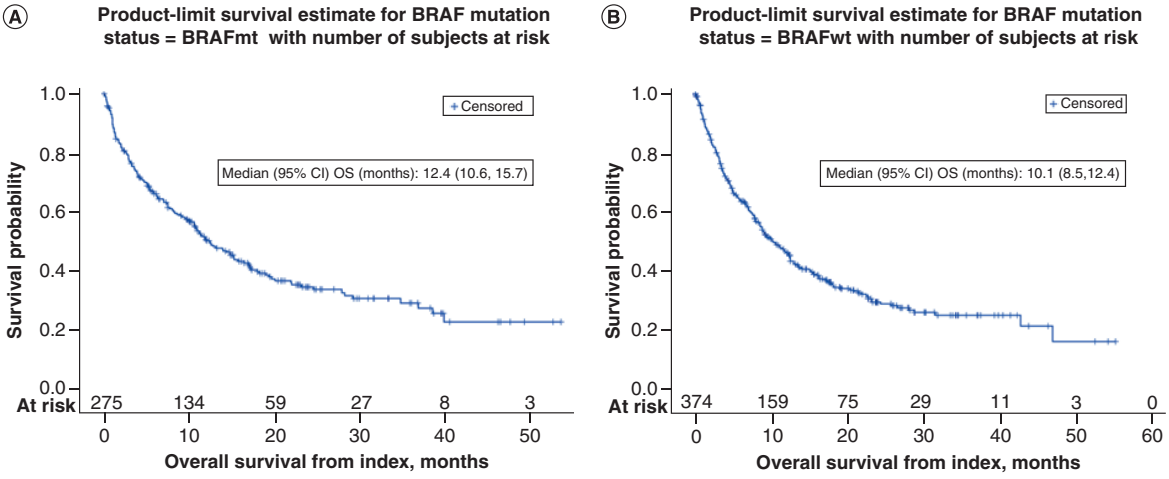

Figure 4. Overall survival from the index date, by *BRAF* status. The index date was the date of disease progression on the index anti-PD-1 line of therapy.
mt: Mutation; OS: Overall survival; wt: Wild-type.

After the index disease progression event recorded in the database, further treatment with the index anti-PD-1 (i.e., treatment beyond disease progression) occurred in 48.4% of patients. Among patients who later initiated a new LOT of any type, before initiating the subsequent therapy, 40.7% continued their anti-PD-1 treatment following disease progression for a median of 1.3 months (Table 2). Among patients who did not go on to receive a subsequent therapy, 59.3% continued their anti-PD-1 treatment after disease progression for a median of 8.8 months.

Overall survival

The median OS from the index disease progression date was 12.4 months (95% CI: 10.6–15.7) in the primary analysis, which includes only those 275 patients with an identified disease progression date (Figure 4).

Subgroup analyses in patients with prior *BRAF* treatment

Analyses were also conducted on the subgroup of patients who received *BRAF* targeted treatment during or before their index anti-PD-1 LOT; however, due to the small sample size (n = 78), results should be interpreted with caution. After discontinuing their index LOT, 43.6% had a subsequent treatment (Supplementary Table 1). The median OS after the disease progression event during the first anti-PD-1 line among these patients was only 5.4 months (Supplementary Figure 1).

Sensitivity analysis for OS in patients who died without a record of disease progression

An index disease progression date was imputed for 114 patients with *BRAF*mt where an index date could not be established because death occurred without a record of disease progression. The median age of these patients was 65.7 years (Supplementary Table 2), and 34.2% had a recorded ECOG score of >1 (Supplementary Table 3). For

more than half of patients (57.0%), the index anti-PD-1 LOT was their first LOT, and 35.1% of patients had one prior LOT. The most common therapies received in prior lines were *BRAF* therapy, alone or in combination with an *MEK* inhibitor (39.5%) and anti-CTLA-4 alone (4.4%; Supplementary Table 4).

For these 114 patients with an imputed date of disease progression, 72 died before or on the median time to disease progression date, and therefore, by definition, had a survival time of 0 days. For the remaining 42 patients, survival time was also limited, with a median time of 2.4 months from imputed disease progression date to death. When adding the patients with an imputed index disease progression date to the primary cohort, the median OS was reduced from 12.4 to 5.7 months (95% CI: 3.9–8.1).

Sensitivity analysis for patients with further treatment with the anti-PD-1 beyond progression

Median OS for patients who received at least one dose of their index anti-PD-1 after their progression event was 24.6 (95% CI: 16.5–not available) months and was 8.0 (95% CI: 5.3–10.7) months for those whose index anti-PD-1 therapy ended on or before the progression date (Supplementary Table 5).

BRAFwt cohort

Baseline demographic & clinical & treatment characteristics

The *BRAF*wt cohort included 374 patients (Figure 1). The median age was 71 years. Stage at initial diagnosis was recorded for 82.4% of patients, with 8.0% stage I, 20.3% stage II, 17.1% stage III, 36.6% stage IV and 0.3% (one patient) with stage 0. Brain metastases were recorded in 17.4% of patients before the date of disease progression (Table 1).

The index LOT was the first LOT for 91.7% of patients. Before the index LOT, anti-CTLA-4 monotherapy was the most common treatment received (7.2%; Figure 3). For their index LOT, approximately one-third of patients received nivolumab monotherapy (36.9%), pembrolizumab monotherapy (31.0%) or nivolumab plus ipilimumab combination therapy (30.5%; Figure 3). The median time from start of the index LOT until the disease progression date was 3.0 months.

First subsequent therapy treatment patterns

After their index LOT, more than half of the patients with *BRAF*wt (61.0%) received no subsequent therapy. Anti-CTLA-4 plus anti-PD-1 (10.7%) or an anti-PD-1 switch (8.6%; from the initial to an alternative anti-PD-1) were the most common treatments for those patients who did receive a subsequent therapy. After the index disease progression event, 57.8% of patients received further treatment with the index anti-PD-1. Among patients who later received a subsequent therapy, 49.3% continued their anti-PD-1 treatment following the record of disease progression, for a median of 2.3 months (Table 2). However, among patients who did not later receive a subsequent therapy, 63.2% continued their anti-PD-1 treatment for a median of 6.2 months following disease progression.

Overall survival

For those with a recorded disease progression date (n = 374), the median OS from the index disease progression date was 10.1 months (95% CI: 8.5–12.4; Figure 4).

Sensitivity analysis for OS in patients who died without a record of disease progression

In the sensitivity analysis, an index disease progression date was imputed for the 194 patients who did not have a record of disease progression. The median age of these patients was 76 years (Supplementary Table 2), and ECOG scores were 2 or higher for 37.1% of patients (Supplementary Table 3). The anti-PD-1 index line was the first LOT for nearly all patients (95.4%), with only 4.1% having had one prior line. The most common treatment received in prior lines was anti-CTLA-4 alone (4.6%; Supplementary Table 4).

Of the 194 patients whose date of disease progression was imputed, 107 died on or before this date and had a survival time of 0 days. The remaining 87 patients had a median survival time of 4.6 months from imputed disease progression date to death. Median OS for the full cohort plus the patients with an imputed index disease progression date was 5.2 months (95% CI: 4.4–6.8), reduced from 10.1 months in the primary cohort.

Sensitivity analysis for patients with further treatment with the anti-PD-1 beyond progression

For patients with *BRAF*wt who received at least one dose of their index anti-PD-1 after progression, median OS was 13.5 (95% CI: 11.1–18.0) months; patients without further treatment with their index anti-PD-1 therapy post-progression had a median OS of 5.8 (95% CI: 3.8–7.9) months (Supplementary Table 5).

Discussion

This retrospective cohort study using real-world data from Flatiron Health provides information on the treatment patterns and OS of patients with advanced melanoma following disease progression on anti-PD-1 treatment. Our findings show that 53.5% of all patients – more than 40% of *BRAF*mt and more than 60% of *BRAF*wt – did not initiate another treatment regimen within the Flatiron system after a record of disease progression on anti-PD-1. Compared with this finding, previous studies found even higher proportions of patients not receiving a second LOT following first-line anti-PD-1-containing treatment, although documented disease progression on the first LOT was not required and patients may not have received further treatment due to long-term response [21,26]. A Danish retrospective cohort study by Bastholt *et al.* that examined subsequent treatment patterns following discontinuation of first-line pembrolizumab in patients with metastatic melanoma found that 70% of patients did not initiate another treatment in the second line [26]. Moser *et al.*, who conducted a retrospective study using data from Flatiron Health to assess treatment patterns and survival among patients with *BRAF*mt advanced melanoma, found that 72.2% of patients treated with nivolumab plus ipilimumab and 59.3% of those receiving anti-PD-1 monotherapy in the first line received no subsequent therapy. Median OS for patients treated with first-line anti-PD-1 therapy was 39.5 months; however, because patients did not necessarily progress on the anti-PD-1 therapy, the result is not directly comparable to that of the current study [21].

In the current study, patients with *BRAF*mt melanoma most commonly received *BRAF* inhibitor therapy with or without a *MEK* inhibitor (34%) in their subsequent treatment, whereas anti-CTLA-4 plus anti-PD-1 (9%) and anti-PD-1 switch (9%) were the most common subsequent therapies for patients with *BRAF*wt. The *BRAF*mt treatment patterns are generally consistent with data presented in previous studies. Moser *et al.*, who produced another Flatiron study of patients with *BRAF*mt advanced melanoma, found that *BRAF*/*MEK* inhibitors were the most frequently observed subsequent therapy for patients who received a second line after first-line anti-PD-1 treatment (66%) [21]. Schilling *et al.*, who assessed survival among patients with *BRAF*mt advanced melanoma stratified by first-line therapy, found that among the patients initiating first-line therapy with anti-PD-1, the most common subsequent therapy was *BRAF* therapy plus *MEK* inhibitors (30.6% of those receiving a subsequent systemic therapy) [22]. Previous studies examining subsequent treatment patterns without stratifying patients by *BRAF* status have found that retreatment with anti-PD-1 therapy, ipilimumab or a combination of both are often used as subsequent therapies for patients who have failed on prior anti-PD-1 treatment [18–20,23,26]. This is consistent with the most common subsequent treatments for the *BRAF*wt population in the current study.

In the current study, the index anti-PD-1 was the first LOT for approximately 72% of patients with *BRAF*mt melanoma and approximately 90% of patients with *BRAF*wt melanoma. With the availability of targeted therapies, patients with *BRAF*mt have more treatment options than patients with *BRAF*wt. A large proportion (61.0%) of patients with *BRAF*wt had no record of a subsequent therapy, and many of these patients (57.8%) had at least one administration of their index anti-PD-1 following the disease progression event. Of those who did receive a subsequent therapy, 9% had an anti-PD-1 switch, which may reflect insufficient treatment options, especially for *BRAF*wt melanoma. Fortunately, newer treatment options for advanced melanoma after progression on anti-PD-1 therapy are in development, including new immunotherapies, such as LAG-3-targeted monoclonal antibodies [27], TIM-3 [28], GITR antibodies [29] and TLR9 agonists [30,31]. Oncolytic viruses, such as talimogene laherparepvec (T-VEC) [32,33], in combination with other therapies are also under investigation [34]. Recently, the phase III DREAMseq study found that in patients with treatment-naive *BRAF*mt, nivolumab plus ipilimumab given before dabrafenib plus trametinib was associated with longer OS (2-year rate of 72 vs 52% in patients who received the opposite sequence). These findings suggest that starting the treatment sequence for *BRAF*mt melanoma with immunotherapy rather than targeted therapy may extend OS for many patients [35,36].

After disease progression on anti-PD-1, median survival was approximately 12 months for patients with *BRAF*mt and 10 months for those with *BRAF*wt in the current study. However, a sensitivity analysis including the >30% of patients who died without a record of disease progression reduced those estimates to nearly 6 months for those with *BRAF*mt and 5 months for those with *BRAF*wt. A recent retrospective study by Patrinely *et al.* examining clinical outcomes of patients with advanced melanoma after disease progression on anti-PD-1 therapy found median OS to be 6.8 months [23]. However, the investigators included a systematic assessment of disease progression using Response Evaluation Criteria in Solid Tumors (RECIST) criteria rather than evaluating clinical notes retrospectively indicating disease progression, which may have resulted in an initial cohort more similar to the current study's sensitivity analysis that includes patients who died without a record of disease progression. Although OS post-disease

progression in the primary cohort of the current study was close to 1 year, the inclusion of patients who died without a record of disease progression produces far less optimistic results. Death of patients before disease progression is captured does occur in clinical practice, in part due to incomplete documentation of disease progression in the real-world setting. In other cases, the death may have occurred too quickly between visits so that disease progression was never observed in the clinical practice. Some of the deaths may have been unrelated to disease progression, where disease progression never occurred, although this is less likely in this population.

The primary analysis of this study might be more reflective of the experience of patients who may be eligible for further treatment, whereas the sensitivity analysis may capture patients who exhibit primary resistance to anti-PD-1 therapies and die without having the opportunity to receive further treatment. Patients who died without a record of disease progression were slightly older on average than the primary cohort, more likely to have been diagnosed at stage IV and more likely to have an ECOG score >1. The sensitivity analysis may better demonstrate the reality of poor survival and unmet need in those patients who experience disease progression on anti-PD-1 therapies [10] with few remaining effective treatment options available to them. Overall, these findings highlight the need for more effective treatments for advanced melanoma.

This analysis of real-world patients provides insights into the treatment patterns and survival of patients with advanced melanoma who progressed on anti-PD-1 therapy treated in community practices. Unlike in clinical trials, a benefit of this study is that there were less stringent inclusion criteria. In addition, post-disease-progression survival has rarely been investigated previously; therefore, this study can serve as a benchmark for future research.

However, it should be noted that disease progression as measured in medical records may capture the real clinical experience of trying to determine whether disease progression actually occurred, but disease progression is not systematically assessed per protocol and may be erroneous in both fact and date of disease progression. The frequent occurrence of continuing treatment with the anti-PD-1 therapy beyond progression suggests that physicians likely saw some ongoing benefit to the treatment despite the apparent evidence of progression, again highlighting that this real-world progression is substantially different from progression examined in clinical trials. The longer OS for patients with treatment beyond progression relative to those without substantiates this notion. Further limitations of this analysis include the lack of information on reasons for treatment decisions, missing data on any care that occurred outside of the oncology clinic 1 and poor recording of comorbidities that were not treated by the oncologist. Patients who sought care in a different oncology clinic or academic center, potentially due to participation in a clinical trial, may have received further treatment that does not appear in the database; thus, the proportion of patients receiving no subsequent therapy may be overestimated. The use of an ICD-10 code to identify brain metastases identified some patients but was likely under-recorded; care should be taken when interpreting these numbers because the absence of the code does not necessarily mean that brain metastases were not present. The majority of Flatiron's data comes from community practice types (90% for the current study). It should be noted that treatment pathways are defined slightly differently in academic versus community centers. The heterogeneity of available treatment options during the cohort selection period, which extends back to 2014, should also be noted as a possible weakness of the study because advances in the treatment of this patient population have been made in recent years.

Conclusion

This real-world retrospective analysis of patients with advanced melanoma treated in the USA revealed that more than 40% of patients with *BRAF*mt and 60% of patients with *BRAF*wt did not initiate a new treatment regimen after disease progression on anti-PD-1 therapies. The median OS after disease progression on anti-PD-1 was 12.4 and 10.1 months for patients with *BRAF*mt and *BRAF*wt, respectively. This may be an overestimate because it excluded patients who died before a clinical record of disease progression was captured in the data source; when these patients are included with those from the primary cohort, median OS is reduced to 5.7 and 5.2 months for patients with *BRAF*mt and *BRAF*wt, respectively. These results highlight the lack of treatment options for patients with advanced melanoma who progress on anti-PD-1-based therapy.

Summary points

- Real-world treatment patterns and outcomes after progression on anti-PD-1-based therapies for melanoma are unknown.
- This retrospective, observational study used the Flatiron oncology electronic medical record database to assess the treatment patterns and overall survival (OS) of patients with advanced melanoma following progression on anti-PD-1 treatment.
- Median OS after progression was 11.3 months (95% CI: 9.9–12.5) overall, 12.4 months (95% CI: 10.6–15.7) for patients with a *BRAF* mutation (*BRAF*mt) and 10.1 months (95% CI: 8.5–12.4) for patients with *BRAF* wild-type (*BRAF*wt).
- For patients with *BRAF*mt, the most common subsequent therapy was *BRAF*-targeted therapy, alone or in combination with a mitogen-activated protein kinase inhibitor (36.7%), but 41.1% of patients had no record of a subsequent treatment.
- A new anti-PD-1-based regimen was the most common subsequent treatment for *BRAF*wt (19.3%), but 61.0% had no record of a subsequent therapy.
- The high proportion of patients receiving no further treatment after progression on anti-PD-1 therapy (other than potentially through a clinical trial), paired with relatively short survival durations, highlight the need for additional treatment options for advanced melanoma.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2021-0340

Author contributions

B Nordstrom, M Hamilton, J Collins, Y Zhang and L Hernandez-Aya contributed to study design, data interpretation and critical review of the results and manuscript. D Earle and S Srivastava contributed to data interpretation and critical review of the results and manuscript. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Ethical conduct of research

The authors confirm that all study data were fully compliant with US patient confidentiality requirements, including the Health Insurance Portability and Accountability Act (HIPAA) of 1996. The study used only deidentified patient records and therefore was exempted from Institutional Review Board approval. Informed consent was not required because this was not an interventional study, and routinely collected, anonymized data were used.

Open access

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Surveillance Epidemiology and End Results Program. SEER Cancer Statistics Review, 1975–2017. Based on November 2019 SEER data submission. In: *SEER Cancer Statistics Review.* Howlader NNA, Krapcho M, Miller D *et al.*. (Eds). National Cancer Institute, MD, USA (2020).
2. Linos E, Swetter SM, Cockburn MG *et al.* Increasing burden of melanoma in the United States. *J. Invest. Dermatol.* 129(7), 1666–1674 (2009).
3. Surveillance Epidemiology and End Results Program. *SEER Cancer Stat Facts: Melanoma of the Skin.* National Cancer Institute, MD, USA (2018).
4. Dalmau E, Armengol-Alonso A, Munoz M, Segui-Palmer MA. Current status of hormone therapy in patients with hormone receptor positive (HR+) advanced breast cancer. *Breast* 23(6), 710–720 (2014).
5. Alsaab HO, Sau S, Alzhrani R *et al.* PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: mechanism, combinations, and clinical outcome. *Front. Pharmacol.* 8, 561 (2017).
6. Ascierto PA, Kirkwood JM, Grob J-J *et al.* The role of BRAF V600 mutation in melanoma. *J. Transl. Med.* 10(1), 85 (2012).
7. Flaherty KT, Infante JR, Daud A *et al.* Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N. Engl. J. Med.* 367(18), 1694–1703 (2012).
8. Larkin J, Ascierto PA, Dréno B *et al.* Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N. Engl. J. Med.* 371(20), 1867–1876 (2014).
9. Whitman ED, Liu FX, Cao X *et al.* Treatment patterns and outcomes for patients with advanced melanoma in US oncology clinical practices. *Future. Oncol.* 15(5), 459–471 (2019).
10. Gide TN, Wilmott JS, Scolyer RA, Long GV. Primary and acquired resistance to immune checkpoint inhibitors in metastatic melanoma. *Clin. Cancer. Res.* 24(6), 1260–1270 (2018).

• **This review examines the mechanisms of primary and acquired resistance to immunotherapy in melanoma.**

11. Philips GK, Atkins M. Therapeutic uses of anti-PD-1 and anti-PD-L1 antibodies. *Int. Immunol.* 27(1), 39–46 (2015).
12. Tumeh PC, Harview CL, Yearley JH *et al.* PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature* 515(7528), 568–571 (2014).
13. Larkin J, Chiarion-Sileni V, Gonzalez R *et al.* Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N. Engl J. Med.* 381(16), 1535–1546 (2019).
14. Larkin J, Chiarion-Sileni V, Gonzalez R *et al.* Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N. Engl. J. Med.* 373(1), 23–34 (2015).
15. Robert C, Long GV, Brady B *et al.* Nivolumab in previously untreated melanoma without BRAF mutation. *N. Engl. J. Med.* 372(4), 320–330 (2015).
16. Robert C, Schachter J, Long GV *et al.* Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N. Engl. J. Med.* 372(26), 2521–2532 (2015).
17. Postow MA, Chesney J, Pavlick AC *et al.* Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N. Engl. J. Med.* 372(21), 2006–2017 (2015).
18. Baron K, Moser JC, Patel S *et al*. Comparative effectiveness of second-line ipilimumab vs. nivolumab in combination with ipilimumab in patients with advanced melanoma who received frontline anti-PD-1 antibodies. *J. Oncol. Pharm. Pract.* 27(3), 555–559 (2020).

•• **A study using electronic medical record data from Flatiron Health to examine the use of ipilimumab monotherapy versus ipilimumab + nivolumab combination therapy after progression on first-line anti-PD-1 therapy.**

19. Nomura M, Otsuka A, Kondo T *et al.* Efficacy and safety of retreatment with nivolumab in metastatic melanoma patients previously treated with nivolumab. *Cancer. Chemother. Pharmacol.* 80(5), 999–1004 (2017).
20. Zimmer L, Apuri S, Eroglu Z *et al.* Ipilimumab alone or in combination with nivolumab after progression on anti-PD-1 therapy in advanced melanoma. *Eur. J. Cancer.* 75, 47–55 (2017).
21. Moser JC, Chen D, Hu-Lieskovan S *et al.* Real-world survival of patients with advanced BRAF V600 mutated melanoma treated with front-line BRAF/MEK inhibitors, anti-PD-1 antibodies, or nivolumab/ipilimumab. *Cancer. Med.* 8(18), 7637–7643 (2019).

•• **This retrospective study used electronic medical record data from the Flatiron database to examine subsequent therapies received and the overall survival of patients who had received first-line anti-PD-1 therapy.**

22. Schilling B, Martens A, Geukes Foppen MH *et al.* First-line therapy-stratified survival in BRAF-mutant melanoma: a retrospective multicenter analysis. *Cancer. Immunol. Immunother.* 68(5), 765–772 (2019).

• **A retrospective study assessing subsequent therapies and survival among patients with BRAFmt advanced melanoma stratified by first-line therapy, including anti-PD-1 agents.**

23. Patrinely Jr JR, Baker LX, Davis EJ *et al*. Outcomes after progression of disease with anti–PD-1/PD-L1 therapy for patients with advanced melanoma. *Cancer* 126(15), 3448–3455 (2020).

•• **This study used electronic medical records to examine clinical outcomes after progression on anti-PD-1 therapy in patients with advanced melanoma.**

24. Da Silva IPAT, Lo S, Reijers ILM *et al.* Ipilimumab (IPI) alone or in combination with anti-PD-1 (IPI + PD1) in patients (pts) with metastatic melanoma (MM) resistant to PD1 monotherapy. *J. Clin. Oncol.* 38(Suppl. 15), 10005–10005 (2020).

•• **This study examined overall survival in patients retreated with immunotherapy following disease progression on initial anti-PD-1 therapy.**

25. Flatiron Health. For Life Sciences (2021). https://flatiron.com/real-world-evidence/

26. Bastholt L, Schmidt H, Bjerregaard JK *et al.* Age favoured overall survival in a large population-based Danish patient cohort treated with anti-PD1 immune checkpoint inhibitor for metastatic melanoma. *Eur. J. Cancer*119, 122–131 (2019).

• **This Danish retrospective cohort study examined subsequent treatment patterns following discontinuation of first-line pembrolizumab in patients with metastatic melanoma.**

27. Ascierto PA, Melero I, Bhatia S *et al.* Initial efficacy of anti-lymphocyte activation gene-3 (anti–LAG-3; BMS-986016) in combination with nivolumab (nivo) in pts with melanoma (MEL) previously treated with anti–PD-1/PD-L1 therapy. *J. Clin. Oncol.* 35, 9520–9520 (2017).

28. Mach N, Curigliano G, Santoro A *et al.* 1202P – phase (Ph) II study of MBG453 + spartalizumab in patients (pts) with non-small cell lung cancer (NSCLC) and melanoma pretreated with anti-PD-1/L1 therapy. *Ann. Oncol.* 30, v491–v492 (2019).

29. Papadopoulos KP, Autio KA, Golan T *et al.* Phase 1 study of MK-4166, an anti-human glucocorticoid-induced tumor necrosis factor receptor (GITR) antibody, as monotherapy or with pembrolizumab (pembro) in patients (pts) with advanced solid tumors. *J. Clin. Oncol.* 37, 9509–9509 (2019).

30. Milhem M, Gonzales R, Medina T *et al.* Abstract CT144: Intratumoral toll-like receptor 9 (TLR9) agonist, CMP-001, in combination with pembrolizumab can reverse resistance to PD-1 inhibition in a phase Ib trial in subjects with advanced melanoma. Presented at: *The American Association for Cancer Research Annual Meeting*. IL, USA (2018).

31. Ribas A, Medina T, Kummar S *et al.* SD-101 in combination with pembrolizumab in advanced melanoma: results of a phase ib, multicenter study. *Cancer Discov.* 8(10), 1250–1257 (2018).

32. Andtbacka RHI, Collichio F, Harrington KJ *et al.* Final analyses of OPTiM: a randomized phase III trial of talimogene laherparepvec versus granulocyte-macrophage colony-stimulating factor in unresectable stage III–IV melanoma. *J. Immunother. Cancer.* 7(1), 145 (2019).

33. Chesney J, Puzanov I, Collichio F *et al.* Randomized, open-label phase II study evaluating the efficacy and safety of talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone in patients with advanced, unresectable melanoma. *J. Clin. Oncol.* 36(17), 1658–1667 (2018).

34. Babacan NA, Eroglu Z. Treatment options for advanced melanoma after anti-PD-1 therapy. *Curr. Oncol. Rep.* 22(4), 38 (2020).

35. Atkins MB, Lee SJ, Chmielowski B *et al.* DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing): a phase III trial–ECOG-ACRIN EA6134. *J. Clin. Oncol.* 39(Suppl. 36), 356154–356154 (2021).

36. Cavallo J. Immunotherapy followed by targeted therapy yields greater overall survival in patients with BRAF V600-mutated advanced melanoma. *ASCO Post.* (2021). https://ascopost.com/news/november-2021/immunotherapy-followed-by-targeted-therapy-yields-greater-overall-survival-in-patients-with-braf-v600-mutated-advanced-melanoma/